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Oral potassium iodide for the treatment of sporotrichosis (Review)

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[Intervention Review]

Oral potassium iodide for the treatment of sporotrichosis

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ABSTRACT

Background

Sporotrichosis is a subacute or chronic disease, usually affecting the skin caused by a dimorphic (existing in two forms), aerobic (oxygen requiring) fungus called *Sporothrix schenckii*. Oral potassium iodide is widely used for cutaneous sporotrichosis in clinical medicine with more and more reports published. However, the benefits and adverse reactions of these treatments have not yet been systematically reviewed.

Objectives

To assess the effects of oral potassium iodide for the treatment of sporotrichosis.

Search methods

In July 2009 we searched the Cochrane Skin Group Specialised Skin Register, the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) in *The Cochrane Library* (Issue 3, 2009), MEDLINE and EMBASE, The Chinese Biomedical Database, CNKI, VIP, and ongoing trials registers.

Selection criteria

Randomised trials comparing orally administered iodide with placebo, or with another treatment. Studies about potassium iodide as an adjunct were excluded.

Data collection and analysis

Two authors planned to independently assess trial quality and extract data. We also planned to collect adverse effects information from the trials where possible.

Main results

In the absence of any suitable randomised placebo-controlled trials or comparisons with other treatments in this area, we were unable to assess the effects of oral potassium iodide.

Authors' conclusions

The currently available evidence is insufficient to assess the potential for oral potassium iodide in the treatment of sporotrichosis.

There is no high-quality evidence for or against oral potassium iodide as a treatment for sporotrichosis. Further randomised double-blind placebo-controlled trials are needed to define the efficacy and acceptability of these interventions.

PLAIN LANGUAGE SUMMARY

Oral potassium iodide for the treatment of sporotrichosis

Potassium iodide is an anti-fungal drug listed in the World Health Organization (WHO) essential drug list and generally thought to be the first choice for cutaneous sporotrichosis including fixed and lymphocutaneous types, in developing countries. No randomised controlled trials (RCTs) of oral potassium iodide versus placebo were found and thus its efficacy and safety could not be analysed in this review. There is a need for randomised placebo controlled trials of oral potassium iodide in this area.

BACKGROUND

Sporotrichosis is a subacute or chronic disease, usually affecting the skin caused by a dimorphic (existing in two forms), aerobic (oxygen requiring) fungus called *Sporothrix schenckii* (Centers for Disease Control and Prevention 2004). The lesions may spread along the lymph channels.

Description of the condition

Etiology and epidemiology

The fungus exists in sphagnum moss, hay, other plant materials, and in the soil (Fitzpatrick 2001). It enters the skin through small cuts or punctures from thorns, barbs, pine needles, or wires but is not spread from person to person. People working in horticulture e.g. tree surgeons, rose gardeners, greenhouse workers, farmers and others working on the soil, are at risk of getting sporotrichosis. It occurs worldwide in people of all ages and races and is observed more often in people aged between 20 and 50 years (Feuerman 1976; Laur 1979; Rajendran 1990; Sherertz 1992; Chakrabarti 1994; Carr 1995; Bonifaz 1999; Wu 1999; Haddad 2002). The countries with the highest reported rates of infection are Mexico, Brazil, and South Africa (Hay 2003).

Clinical features and diagnosis

The clinical types of sporotrichosis are divided into four groups: fixed cutaneous, lymphocutaneous, cutaneous disseminated, and extracutaneous (Wiederman 1992).

1. Fixed cutaneous: infections are confined to a localised area of the skin. A nodule arises one to two weeks after infection, then slowly enlarges and frequently breaks down to form an ulcer.
2. Lymphocutaneous: infections will spread along lymphatic vessels to cause lesions along the lymph channels after development of the primary lesion.
3. Cutaneous disseminated: spread to other areas of the skin beyond the draining lymph node vessels as may happen in AIDS.
4. Extracutaneous: when the infection spreads from the skin to other internal sites of the body such as joints and bones, eyes and the central nervous system.

Systemic and disseminated sporotrichosis are uncommon but may follow the spread of infection from lymphocutaneous disease, sometimes involving joints, lungs, or the central nervous system (Sherertz 1992; Hay 2003).

The diagnosis of sporotrichosis should be based on culturing the organism from tissue or fluid obtained from infected sites (Stonecipher 1997). Histopathology may be helpful but is not diagnostic. Immunodiffusion tests (antigen-antibody reaction) may be helpful.

Natural history

The vast majority of infections are limited to the skin and the infections slowly get worse, but are rarely fatal. There are no reports of spontaneous resolution without treatment. Cases of joint, lung, and central nervous system infection have occurred but are very rare and usually occur only in people with diabetes or other disorders of the immune system (New York State 2004).

Description of the intervention

Several forms of treatment have been used, such as potassium iodide or sodium iodide taken by mouth, local heat administration, amphotericin B (an antibiotic) and azole anti-fungal drugs. Potassium iodide is an anti-fungal drug listed in the WHO essential drug list (WHO 2002) and generally thought to be the first choice for cutaneous sporotrichosis, including fixed and lymphocutaneous types, in developing countries (Wu 2000). Local heat administration is considered as an adjunctive treatment and may be particularly effective in the early stages of infection with mild tissue injury. Amphotericin B is the traditional choice for systemic sporotrichosis. Azole anti-fungal drugs including ketoconazole, itraconazole, and terbinafine are recommended for those people who have severe reactions to iodide, but these drugs are expensive and the period of treatment is long, so they are not widely used in high-prevalence areas of the developing world (Lu 2000).

Oral potassium iodide in the treatment of sporotrichosis

Five years after the first reported case of sporotrichosis in 1898, a series of reports began to appear in France which described its treatment with potassium iodide (Hay 2003). Although this simple chemical has been used for about 100 years, the mechanism of action is not clearly understood. It has been demonstrated that a saturated solution of potassium iodide (SSKI) shows no activity in vitro in the laboratory against *Sporothrix schenckii* (Jones 1991), so it does not kill *Sporothrix schenckii* directly. It is now thought that macrophages (normal scavenger cells), can be stimulated by potassium iodide to inhibit growth of the fungus (Li 2001). However, there are some Japanese and Indian studies that do show a direct anti-fungal effect (Sandhu 2003; Shinogi 2004).

A saturated solution of potassium iodide is administered in a slowly ascending dose beginning with 3 drops 3 times per day increasing until limited by adverse effects, or until a clinical response is achieved or until a maximum dose of roughly 40 drops per day is reached, (equivalent to 400 mg of iodine) (Jones 1991). The medication is relatively cheap but is unpalatable.

Contraindications include: hypersensitivity to iodide, acute bronchitis or acute tuberculosis, and pregnancy (Jones 1991). Side-effects are common and include acne-like spots, nausea, vomiting, parotiditis (inflammation of the parotid gland), and hypothyroidism (reduced activity of the thyroid gland). Usually the adverse effects are mild and can be curtailed by decreasing the dosage or temporarily stopping the administration of the drug (Wiederman 1992).

Why it is important to do this review

Oral potassium iodide is widely used for cutaneous sporotrichosis in clinical medicine with more and more reports published. However, the benefits and adverse reactions of these treatments have not yet been systematically reviewed.

OBJECTIVES

To assess the effects of oral potassium iodide for the treatment of sporotrichosis.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Anyone who has been diagnosed with definite sporotrichosis, based on a positive culture of the fungus in a sample obtained from an involved site, serum, or cerebrospinal fluid. An immunodiffusion test may also be used to further support the diagnosis.

Types of interventions

Orally administered iodide compared with placebo, or with another treatment. Studies in which potassium iodide was used as an adjunct were excluded.

Types of outcome measures

Primary outcomes

Proportion of participants with clinical cure. Clinical cure is defined as an absence of clinical symptoms together with negative diagnostic tests (negative findings from histopathology, immunodiffusion tests, or culturing the organism from tissue or fluid obtained from infected sites).

Secondary outcomes

1. Proportion with good or excellent improvement as rated by the participant or doctor.
2. Severe adverse events i.e. severe enough to require withdrawal of treatment.
3. Changes in quality of life scores.

Good or excellent improvement was defined as lesions that had been localised and the clinical symptoms cleared up.

We compared outcomes mentioned above at the time points less than or equal to four weeks (short-term), more than four weeks to six months (medium-term) and longer-term (more than six months), depending on data.

Tertiary outcome measures

1. Change in isolation rate of sporotrichosis from baseline to assessed follow-up time.
2. Change in fungal counts of sporotrichosis from baseline to assessed follow-up time (i.e. an assessment of quantity of sporotrichosis).
3. Changes in the individual signs of sporotrichosis as assessed by a physician from baseline to assessed follow-up time (e.g. size of lesion, presence of ulceration).
4. Duration of remission or prevention of subsequent flares, or both.
5. Minor adverse events reported by the participants, not sufficient to require withdrawal of treatment.

Search methods for identification of studies

Electronic searches

We searched the following databases:

- The Cochrane Skin Group Specialised Register (21st July 2009) using the following search terms: (sporotrichosis or sporothrix or sporotrich* or *trichos*) AND (potassium and iodide).
- The Cochrane Central Register of Controlled Clinical Trials in *The Cochrane Library* Issue 3, 2009 using the search strategy in [Appendix 1](#).
- MEDLINE (from 1966 to 21st July 2009) using the strategy in [Appendix 2](#).
- EMBASE (from 1980 to 21st July 2009) using the strategy in [Appendix 3](#).
- Chinese Biomedical Database (from 1976 to 22nd July 2009).
- Chinese National Knowledge Infrastructure (CKNI) (1979 to 22nd July 2009).
- VIP (1988 to 22nd July 2008).

Ongoing Trials

We also searched the following registries (22nd July 2009) by using the term 'sporotrichosis' for ongoing trials:

- National Research Register (www.nrr.nhs.uk/)
- The metaRegister of Controlled Trials (www.controlled-trials.com/)
- The U.S. National Institutes of Health Ongoing Trials Register www.clinicaltrials.gov
- Chinese Clinical Trial Register (www.chictr.org/tr)
- The Australian and New Zealand Clinical Trials Registry www.anzctr.org.au
- WHO International Clinical Trials Registry Platform (ICTRP) search portal (www.who.int/trialsearch/)
- The Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials)

Searching other resources

Unpublished literature

Due to a lack of resources we were unable to search for unpublished literature as we had originally planned, so we did not correspond with trial authors or contact pharmaceutical companies.

Conference proceedings

We did not search conference proceedings as we had planned in the protocol due to lack of resources.

Adverse effects

We conducted a search for side-effects, however we made no valuable findings.

Language restrictions

We imposed no language restrictions when searching for publications.

Data collection and analysis

Two authors (XSL and GR) performed data collection and analysis. One author (WTX) checked the search results.

Selection of studies

Titles and abstracts identified from the searches were checked independently by two authors (XSL and GR). Studies not referring to

a randomised controlled trial on sporotrichosis were excluded. The authors decided which trials fitted the inclusion criteria through discussion.

None of the studies were identified as randomised controlled trials suitable for inclusion from our search.

There was no disagreement.

Data extraction and management

No studies were included for data extraction and management. If in future updates of this review any study is eligible for inclusion, two of us (XSL and GR) will extract data using a data extraction form, specifically designed for this review.

If we find RCTs suitable for inclusion in a future update then two authors (XSL and WXS) will independently abstract the data. We will then resolve differences in data extraction by discussion and by reference to the original article. Where necessary, we will seek information from the trial authors of the primary studies. Where there is any disagreement we will consult a third author (WTX) to resolve this.

Missing data will be obtained from authors where possible. Data will be checked and entered into RevMan by one reviewer (XSL). The authors will not be blinded to the names of trialists, journal, or institutions.

Assessment of risk of bias in included studies

In the future, if there is any study included in the review, we will assess the methodological quality of each trial in terms of generation of allocation sequence, allocation concealment, blinding, incomplete data, and selective reporting; and classify them as 'low risk', 'moderate risk', or 'high risk' according to the guidelines in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008) and as described in Wu 2007.

a) The method of generation of the randomisation sequence; In the future, if there is any study included in the review, an adequate approach for generating an allocation sequence with low risk of selection bias should be a random number table or computer software, and other simple random methods, for example, coin tossing, shuffling. All of the methods for generating the allocation sequence should be used before recruiting the participants.

Any future trial which only mentioned 'random' but lacked a description of the approach will be considered as having a moderate risk of selection bias.

b) The method of allocation concealment - it will be considered 'adequate' if the assignment cannot be foreseen; Low risk of selection bias: where measures have been taken to conceal allocation sequence, e.g. where the person who generated an allocation sequence did not attend to recruit the participants, central allocation, and the allocation sequences were conserved safely, for example, sealed in opaque envelopes or conserved in a locked computer, or another description that contains convincing elements of concealment.

Moderate risk of selection bias: where concealment of the allocation sequence was mentioned but the approach has not been reported clearly.

High risk of selection bias: where the concealment of the allocation sequence reported was inadequate, or where there was a possibility that those involved could foresee assignments.

c) Who was blinded/not blinded (participants, clinicians, outcome assessors);

Where both participants and results assessors were masked we will consider those trials as having a low risk of performance or/and detection bias.

We will consider single-blinding for results assessors as a moderate risk of performance or/and detection bias. However, if only the participants were blinded we will consider it as having a high risk of detection bias.

Non-blinding for detection of outcomes include quality of life and adverse events which we will consider as having a high risk of detection bias. The rule of blinding will not be used in reporting of mortality.

d) How many participants were lost to follow-up in each arm and whether reasons for losses were adequately reported;

e) Whether all participants were analysed in the groups to which they were originally randomised (intention-to-treat).

In addition, assessment will be made of the following:

f) Severity of the disease;

g) Baseline comparison for severity of disease.

Measures of treatment effect

In a future update where we have found suitable RCTs we expect both event (dichotomous) data and continuous data. In this case we will analyse different comparisons separately. We will use risk ratios (RR) with 95% confidence intervals (CI) and control events rates for reporting dichotomous data. We will also calculate the number needed to treat (NNT) or the number needed to harm (NNH) if follow-up time and control event rates are similar for the different trials. We will express continuous data as weighted mean differences (WMD) with 95% CI. We will estimate pooled results using a random-effects model (DerSimonin and Laird model).

Dealing with missing data

In a future update of this review where RCTs suitable for inclusion are found we will assess incomplete outcome data for potential bias from exclusions and attrition:

Low risk of bias: trials where few exclusions and attrition are noted and an intention-to-treat analysis is possible.

Moderate risk of bias: trials which reported the rate of exclusions or/and attrition was about 10% whatever intention-to-treat analysis was used.

High risk of bias: the rate of exclusion or/and attrition was higher than 15%, or wide differences in exclusions between groups whatever the intention-to-treat was used.

Assessment of heterogeneity

For an assessment of heterogeneity we will use the I^2 statistic. If we find a trial has moderate levels of heterogeneity ($I^2 > 50\%$) for the primary outcomes, we will explore possible sources of

heterogeneity using sensitivity and subgroup analyses as described below.

Assessment of reporting biases

In a future update of this review we will assess potential publication bias using funnel plots or other corrective analytical methods depending on the number of clinical trials included in the update of this systematic review (Egger 1997).

We will assess the reporting bias according to the description in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2008):

No - low risk of reporting bias: if all of the outcomes were reported in detail.

Probably yes - moderate risk of reporting bias: if at least one of the outcomes were mentioned but not in detail.

Yes - high risk of reporting bias: if at least one of the outcomes were not reported.

Data synthesis

In a future update of this review if studies are similar, then we will combine data using meta-analysis techniques.

Subgroup analysis and investigation of heterogeneity

In future updates of this review where RCTs suitable for inclusion are found, we will aim to perform subgroup analyses in order to explore effect size differences between such groups as:

- a) different types of infection, for example: fixed cutaneous, lymphocutaneous, disseminated cutaneous, and extracutaneous;
- b) dose;
- c) duration of disease prior to treatment;
- d) benefit less than or equal to four weeks (short-term), more than four weeks to six months (medium-term) and longer-term (more than six months), depends on data.

Sensitivity analysis

In future updates of this review where RCTs suitable for inclusion are found, we will perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- a) repeating the analysis excluding unpublished studies (if there were any);
- b) repeating the analysis taking account of study quality, as specified above;
- c) repeating the analysis excluding studies using the following filters: language of publication, source of funding (industry versus other), and country;
- d) the robustness of the evidence will be tested by comparing the effects of pooled analysis by random-effect model and fixed-effect model.

We will list non-randomised controlled studies but not discuss them further and we will describe qualitatively any studies relating to adverse effects.

RESULTS

Description of studies

We were unable to include any trial which fulfilled our criteria of oral potassium iodide compared with placebo, or with another treatment. We excluded one study (Cabezas 1996) because the intervention which was a full dose of potassium iodide taken once a day compared to the same dose split over three times a day, did not fulfil our criteria.

Risk of bias in included studies

No trials were included.

Effects of interventions

In the absence of any suitable trial, we unable to perform any analyses.

DISCUSSION

Although, potassium iodide has been widely used for Sporotrichosis for more than 100 years, unfortunately, no randomised placebo-controlled trial has been carried out. This situation reflects the fact that this is an under-researched condition, or maybe that it is very difficult to find participants to take part in trials. Organising trials may also be a challenge since cases may be rare and sporadic. Funding such trials may also be a problem.

AUTHORS' CONCLUSIONS

Implications for practice

There is no good evidence for or against oral potassium iodide as a treatment for sporotrichosis.

Implications for research

Further research on oral potassium iodide in the treatment of Sporotrichosis is needed in order to define its efficacy and acceptability. Ideally any future trial should be of double-blind design in which both the assessor and participants are blinded; outcome measures should include quality of life, duration of cure and adverse events. Adverse events should be critically assessed by standardised monitoring or an effective self-reporting system. Also attention should be paid to long-term adverse effects on the thyroid gland.

ACKNOWLEDGEMENTS

We would like to thank Sue Jessop, Dedee Murell, Jo Leonardi-Bee, Philippa Middleton, and Hywel Williams, editors of the Cochrane Skin Group; Rod Hay, external content expert; Jack Tweed, consumer peer reviewer; Tina Leonard; and Finola Delamere, Managing Editor of the Cochrane Skin Group, for advice in writing this protocol and review.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Cabezas 1996	This RCT did not meet our inclusion criteria of orally administered iodide compared with placebo. The purpose of this study was to compare the safety and efficacy of use of once a day versus three times a day of the daily full dose of potassium iodide.

APPENDICES

Appendix 1. Cochrane Library search strategy

```
#1(sporotrich*)
#2MeSH descriptor Sporotrichosis explode all trees
#3(sporothrix schenckii):ti,ab,kw
#4(sporotrich*):ti,ab,kw
#5*trichos*
#6(#1 OR #2 OR #3 OR #4 OR #5)
#7(oral potassium NEXT iodide):ti,ab,kw
#8(oral SSKI):ti,ab,kw
#9'KI':ti,ab,kw
#10MeSH descriptor Potassium Iodide explode all trees
#11(#7 OR #8 OR #9 OR #10)
#12(#6 AND #11)
```

Appendix 2. MEDLINE search strategy

```
1. randomized controlled trial.pt.
2. controlled clinical trial.pt.
3. randomized.ab.
4. placebo.ab.
5. clinical trials as topic.sh.
6. randomly.ab.
7. trial.ti.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. humans.sh.
10. 8 and 9
11. sporotrichosis.mp. or exp Sporotrichosis/
12. exp Sporothrix/ or sporothrix schenckii.mp.
13. exp Potassium Iodide/ or oral potassium iodide.mp.
14. 'KI'.mp.
15. oral SSKI.mp.
16. 11 or 12
17. 13 or 14 or 15
18. 16 and 10 and 17
```

Appendix 3. EMBASE search strategy

1. random\$.mp.
2. factorial\$.mp.
3. crossover\$.mp.
4. placebo\$.mp. or PLACEBO/
5. (doubl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
6. (singl\$ adj blind\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name]
7. assign\$.mp.
8. volunteer\$.mp. or VOLUNTEER/
9. Crossover Procedure/
10. Double Blind Procedure/
11. Randomized Controlled Trial/
12. Single Blind Procedure/
13. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12
14. sporotrichosis.mp. or exp Sporotrichosis/
15. exp Sporothrix/ or sporothrix schenckii.mp.
16. 14 or 15
17. 13 and 16
18. exp Potassium Iodide/ or oral potassium iodide.mp.
19. oral SSKI.mp.
20. KI.mp.
21. 18 or 19 or 20
22. 17 and 21

HISTORY

Protocol first published: Issue 3, 2006

Review first published: Issue 4, 2009

Date	Event	Description
15 July 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Trial selection quality assessment, data extraction, input and analysis data, and development of the review: Siliang Xue (XSL), Rui Gu (GR), and Taixiang Wu (WTX).

Checking both the data extraction and input, and helping to develop review: Xiaoshan Wang (WXS).

Checking the protocol: Mingming Zhang (ZMM).

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Centre, West China Hospital of Sichuan University, Chinese Medical Board of New York (CMB), China.

External sources

- Cochrane Skin Group, UK.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

1. The quality assessment of included studies section was revised according to the new version of the Cochrane Handbook of Systematic Reviews of Interventions 5.0 ([Higgins 2008](#)).
2. The search strategy section was revised to include searching for ongoing studies in trial registries.
3. Types of studies for inclusion has changed to randomised controlled trials only.

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Antifungal Agents [*administration & dosage]; Potassium Iodide [*administration & dosage]; Sporotrichosis [*drug therapy]

MeSH check words

Humans